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KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET
SUITE #1600
PORTLAND, OR 97204-2988

| EXAMINER | |
|---|---|
| KAUSHAL, SUMESH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/534,626 | FINKEL ET AL. | |
| | Examiner | Art Unit | |
| | Sumesh Kaushal | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16,20-29 and 48-53* is/are pending in the application.

4a) Of the above claim(s) *20-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6 and 48-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response filed on 08/14/07 has been acknowledged and fully considered. Claims 1-16, 20-29, 48-53 are pending.
Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **571-273-8300**

### *Election/Restrictions*

Applicant's election with traverse of Group I (claims 1-16 and 48-50) in the reply filed on 08/14/07 is acknowledged. The traversal is on the ground(s) that Groups I and III share the same special technical feature: detecting alterations in EPCs to detect alterations in vascular function; and the cited art Kalka et al (Cir. Res. 86:1198-1202, 2000, ref of record) does not use the number of EPCs to diagnose a disease, to assess vascular function, or that the number of EPCs are of use in screening for agents of interest. The applicant concludes that Kalka et al does not negate the special technical feature of Groups I and Group III. The applicant requested the reconsideration and rejoinder of Groups I and III.

This is not found persuasive because as stated earlier Kalka et al (Cir. Res. 86:1198-1202, 2000) teaches the invention of group III as the reference teaches the intramuscular injunction of a plasmid encoding VEGF gene, which results in a significant increase in EPCs (21.9%, $P<0.001$). Therefore unity of invention is broken in view of cited art of record, which provides a method to evaluate the effect of an agent on EPCs and vascular function.

The requirement is still deemed proper and is therefore made FINAL.

Claims 20-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 08/14/07.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-6, 9, 16 and 48-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Vasa et al (Circ. Res. 89(1):E1-7, 2001, ref. of record on PTO-1449).

The instant claims are drawn to a method of diagnosing decreased or increased vascular function in a subject by enumerating endothelial progenitor cells in a blood sample from a subject.

Vasa et al teaches number and migratory activity of circulating Endothelial Progenitor Cells (EPCs) inversely correlate with risk factors for coronary artery disease (CAD). The cited art further teaches enumeration of EPCs in CAD patients and normal controls. The cited art teaches the isolation and enumeration of EPCs from the peripheral blood of patients with coronary artery disease (CAD) and compared the results to a control sample (see abstract, page 4, fig(s) 2-4). The cited art teaches that mononuclear cells were isolated by density-gradient centrifugation of peripheral blood (page 2, co.1 para.4). The cited art teaches that circulating EPCs are considered to be characterized by expression of CD34 and the VEGF receptor KDR. The cited art further teaches enumeration of CD34/KDR(VEGFR2$^{+}$) double-positive EPCs, which inherently express CD31(DAKO) (see Vasa page 1, col.1, page 6, col.1 para 2, also see *Asahara et al Science ;275:964–967, 1997, ref of record on PTO1449*). The cited art further teaches that CD34-/KDR-positive cells were significantly reduced by ≈48% in patients with CAD compared with 9 age-matched healthy volunteers (see Fig 4A). The cited art concluded that the number of risk factors was inversely correlated with the levels of CD34-/KDR-positive cells (page 3. col.2 para.2). The cited art further teaches that increased age and elevated LDL cholesterol serum levels significantly correlated with lower numbers of CD34-/KDR-positive cells (Fig 4D and 4E). The cited art further

teaches that that several experimental studies indicate a significant contribution of EPCs for adult neovascularization, the reduction in the number of EPCs and their functional impairment might contribute to reduced vascularization in patients with CAD. The cited art further teaches that age (senescence), hypertension, smoking, cholesterol levels, and a positive family of CAD, as well as the overall number of risk factors, have all been shown to be associated with impaired endothelium-mediated vasodilator function of the coronary circulation. Therefore, one may speculate that the impairment of circulating EPCs may contribute to an insufficient regeneration of the endothelium, which may lead to endothelial dysfunction (page 6, col.1 para 1, table-1). Thus given the broadest reasonable interpretation the cited art clearly anticipates the invention as claimed.

Claims 9-11 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Vasa et al (Circulation. 103(24):2885-90, 2001, ref. of record on PTO-1449).

The instant claims are drawn to a method of diagnosing increased vascular function in a subject by enumerating endothelial progenitor cells in a blood sample from a subject in response to a cholesterol-lowering agent.

Vasa et al teaches increase in circulating EPCs by statin therapy in patients with stable coronary artery disease (CAD). The cited art teaches enumeration of EPCs in patients treated with blood cholesterol lowering agent atorvastatin (page 2888 fig-3, fig-4). The cited art demonstrated that statin therapy is associated with an increase in the number of circulating EPCs in patients with stable CAD. The cited art teaches the isolation and enumeration of EPCs from the peripheral blood of patients with coronary artery disease (CAD) and compared the results to a control sample (see page 2887, fig-2A). The cited art further teaches enumeration of EPCs expressing CD34+/KDR (VEGFR2$^+$) which inherently express CD31(DAKO) (see Vasa page 2887 col.2 para. 2, page 2888, col.1; also see Asahara et al *Science* ;275:964–967, 1997). The cited art further teaches that the results of the present study demonstrate that statin therapy is associated with an increase in the number of circulating EPCs in patients with stable CAD. The increased number of EPCs was paralleled by an enhancement of the migratory capacity of isolated EPCs. Mobilization of circulating EPCs with enhanced

functional activity might contribute to the well-established beneficial effects of statins in patients with CAD as it is well established that EPCs participate in repair after ischemic injury (page 2889, col.1 para. 2). The cited art further teaches that statin therapy has shown to rapidly enhance coronary blood flow in patients with stable CAD and to reduce myocardial ischemia after an acute ischemic episode within a few weeks of treatment (page 2889, col.2 para. 4). Thus given the broadest reasonable interpretation the cited art clearly anticipates the invention as claimed.

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3, 7-8, 12-15 and 48-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 and 12 are indefinite because it is unclear how the number of endothelial progenitor cells that elicits any phenotypic markers are assayed by merely subjecting a mixed population of non-adherent blood cells obtained form buffy coat to any and all kind culture conditions that leads to any and all kinds of colonies derived from any and all kind of cells present in the blood cell preparation as claimed.

Claim 48-50 are indefinite because it is unclear is the "senescent endothelial progenitor cells". The instant claim fails to recite any phenotypic feature that would distinguish the invention as claimed in view of a non- senescent endothelial progenitor cell.

## *Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

**SUMESH KAUSHAL**
**PRIMARY EXAMINER**